UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,455	09/12/2003	Thanyaphong Na Nakorn	STAN-278	4085

24353 7590 01/15/2008

BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER
BARNHART, LORA ELIZABETH

ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
01/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,455	NAKORN ET AL.	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,12 and 13* is/are pending in the application.

4a) Of the above claim(s) *6,9,12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application on 10/26/07 after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/7/07 after final rejection has been entered.

Response to Amendments

Applicant's amendments filed 8/7/07 to claim 1 have been entered. No claims have been cancelled or added in this reply. Claims 1, 4-9, 12, and 13 remain pending in the current application, of which claims 1, 4, 5, 7, and 8 ONLY are being considered on their merits. Claims 6, 9, 12, and 13 remain withdrawn from consideration at this time. Prior art references not included with this Office action can be found in a prior action.

It is noted that claim 9 has been provided with the status identifier "original," but it is actually a withdrawn claim, as set forth in previous Office actions (see, e.g. the final rejection mailed 4/26/07). In the interest of compact prosecution, however, an Office action on the merits will be prepared at this time, since the status of the claim is clear from the prosecution history. Future claim listings with incorrect status will be considered noncompliant with 37 C.F.R. 1.121.

Claim Objections

The objection to claim 1 is withdrawn in light of the amendments.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1 has been amended to require that the monopotent mammalian megakaryocyte precursor cells (MKPs) "give rise exclusively to megakaryocyte colonies." There is no support, either explicit or otherwise, for this limitation in the specification. At page 19 of the as-filed specification, paragraph 79 discusses the properties of MKPs cultured *in vitro* in methylcellulose medium and reads as follows:

> MKPs gave rise mainly to CFU-MK with less than 1% CFU-GM, CFU-M and BFU-E (Table 1). The readouts of these non-megakaryocyte colonies can be totally eliminated by using more restricted sorting gates, indicating that they were derived from the contaminants from the other progenitor pools rather than from MKPs.

Applicant should clarify the basis for the statement that non-megakaryocyte colonies are derived from "contaminants from the other progenitor pools" rather than from MKPs. Claims 4, 7, and 8 are excluded from this rejection because they do not require that the MKPs give rise **exclusively** to megakaryocyte colonies.

The rejections of record under 35 U.S.C. § 112, second paragraph, are withdrawn in light of the amendments to the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 7, and 8 remain rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Clay et al. (2001, *Blood* 97: 1982-1989). The claims are drawn to a composition comprising cells that express CD41, CD9, and CD34, but not 12 other particular markers. In some dependent claims, the cells have various properties when cultured under particular conditions. The claims are also drawn to a method of enriching a cell population for cells that express CD41, CD9, and CD34 comprising contacting a sample of hematopoietic cells with reagents that recognize CD41, CD9, and CD34 and selecting for cells that express CD41, CD9, and CD34. In some dependent claims, the sample of hematopoietic cells is bone marrow.

As discussed above, Clay et al. teach a purified population of cells that express CD41, CD9, and CD34 (Figure 2; page 1985, column 2). These cells were purified using immunomagnetic bead sorting, which comprises contacting human bone marrow mononuclear cells with a hapten-conjugated anti-CD34 antibody and anti-hapten antibody-coated magnetic beads, which yielded a >97% pure population of CD34+ cells

(page 1983, column 1, paragraph 3). These purified CD34+ cells were further contacted with anti-CD9 antibodies and anti-CD41 antibodies and sorted to near purity using a flow cytometer (page 1983, column 1, paragraph 5; Figure 3). The population collected by gate E in Figure 3 is CD34+ $CD9^{high}$ $CD41^{high}$; the population collected by gate D in Figure 3 is CD34+ $CD9^{mid}$ $CD41^{mid/low}$ (page 1985, column 2, paragraph 1). Clay et al. further teach that adding erythropoietin (EPO) to these cells gives rise to BFU-E/MK, megakaryocyte colonies (page 1985, column 2, paragraphs 2-3); the cells of Clay et al. are therefore mammalian megakaryocyte precursor cells.

Regarding the limitation in claim 1 excluding the lack of expression of 12 specific markers, the Patent and Trademark Office is not equipped to conduct experimentation in order to determine whether or not applicants' cell population differs, and if so to what extent, from the cell population discussed in Clay et al. Accordingly, it has been established that the prior art cell population, which expresses CD41, CD9, and CD34 (Figure 3, box E) but not glycophorin A (Figure 1) and has the ability to differentiate to megakaryocyte colonies when treated with EPO, demonstrates a reasonable probability that it is either identical or sufficiently similar to the claimed cell population that whatever differences exist are not patentably significant. Therefore, the burden of establishing novelty or unobviousness by objective evidence is shifted to applicants.

The fact that a characteristic of a known cell population is not disclosed in a reference does not make the known cell population patentable. The instantly claimed cell population possesses inherent characteristics, for example the lack of expression of the markers recited in lines 3 and 4 of claim 1, the response to the agents recited in

claim 4, and the exclusive production of megakaryocyte colonies under some conditions, which might not be displayed in the tests used by Clay et al. Clear substantive evidence (and not merely attorney argument or opinion evidence) that the cell population of the cited prior art does not possess a critical characteristic that is possessed by the claimed cell population would advance prosecution and might permit allowance of claims to applicants' cell population.

Applicants allege that the instant cells were isolated using a lineage panel to select a particular population, and this panel was not employed by Clay et al. (Reply, page 4, paragraph 4). Applicants allege that Clay et al. showed that their cells comprise progenitor cells for mixed erythroid colonies (reply, page 5, paragraph 2). Applicants supply a declaration under 37 C.F.R. 1.132 by Dr. Holger Karsunky (hereafter "the Karsunky declaration") interpreting the results of Clay et al. These arguments have been fully considered, but they are not persuasive.

The instant claims are drawn to a population of cells and only to a population of cells. Clay et al. teach a population of cells that express CD41, CD9, and CD34 but not glycophorin A. The fact that the cells of Clay et al. were not isolated using the same lineage panel as the instant cells is not necessarily evidence that the cells per se are different.

The main point of contention in this application is the differentiation potential of the instant composition compared to that of the prior art. Applicants evaluated the differentiation potential of their $CD34^{+}CD41^{+}CD9^{+}$ cells in METHOCULT M3231 IMDM-based methylcellulose medium (see technical information from StemCell Technologies,

Inc., regarding METHOCULT M3231, http://www.stemcell.com/technical/03231-PIS.pdf; reference U) supplemented with unspecified amounts of SCF, IL-3, IL-11, Flt3 ligand, GM-CSF, erythropoietin, and thrombopoietin (specification, paragraph 0075 on page 18). On the other hand, Clay et al. evaluated the differentiation potential of their $CD34^{+}CD41^{mid}CD9^{mid}$ cells and $CD34^{+}CD41^{high}CD9^{high}$ cells in **another** IMDM-based methylcellulose medium comprising particular amounts of fetal calf serum, bovine serum albumin, 2-mercaptoethanol, L-glutamine, antibiotics, erythropoietin, stem cell factor, IL-1β, IL-3, IL-6, GM-CSF, and G-CSF (page 1983, column 2, paragraph 2). The combinations of differentiation-inducing agents comprised in the two media are distinct. Specifically, applicants' medium includes at least 3 components (IL-11, Flt-3 ligand, and thrombopoietin) that are not present in the medium of Clay et al. Conversely, the medium of Clay et al. includes at least 5 components (BSA, L-glutamine, antibiotics, IL-1β, and G-CSF) that are not present in applicants' medium.

Applicants have provided no evidence that the $CD34^{+}CD41^{+}CD9^{+}$ cells of Clay et al. would not be monopotent in the methylcellulose medium employed in the instant application; in other words, the monopotency of the instantly claimed cells may depend on the medium in which they are cultured, not only on the set of expressed and nonexpressed markers. There is ample evidence on the record to indicate that this is the case. Clay et al. teach that changing the combination of cytokines also changes colony formation in the assay (see the second-to-last sentence of paragraph 2 at page 1983, column 2, discussing reference 25). Indeed, the Karsunky declaration supplied by applicant supports this conclusion, since Dr. Karsunky indicates that the types of

colonies generated by the MKPs of the instant invention vary "depending on the cytokine cocktail used" (see page 2, paragraph 2, of the Karsunky declaration), referring to applicants' own experimental data in Table 2 (page 20 of the as-filed specification). The claims do not require that the MKPs be monopotent under any particular conditions, and applicant's own data and the opinion of experts indicates that MKPs' differentiation properties *in vitro* are modified by variations in growth factors and cytokines in their media.

The Karsunky declaration has been fully considered, but the Dr. Karsunky's comments are limited to an interpretation of the explicit teachings of Clay et al. and do not discuss inherent properties of these cells that may not have been addressed by Clay et al. The inherent properties of the cells of Clay et al. are at issue in this rejection. Specifically, the Karsunky declaration contains no evidence that cells isolated using the method of Clay et al. and cultured in applicants' methylcellulose myeloid differentiation medium described at paragraph 0075 of the instant specification are not monopotent. Because the expression profiles of the cells overlap, the person of ordinary skill in the art would have had a reasonable expectation that the cells of Clay et al. are not patentably distinct from the instantly claimed cells.

Even if, as the Karsunky declaration concludes, Clay et al. "failed to identify the $CD41^+$ population as a potent megakaryocyte progenitor," the rejection would still not be overcome. Applicants have provided insufficient evidence that the cells of Clay et al. are materially different from the instantly claimed cells. The fact that applicants and Clay et al. obtained different experimental results under two different sets of experimental

conditions is not evidence that the cells are patentably distinct. Furthermore, it is noted for the record that claims 4 and 7 do not require that the MKPs give rise **exclusively** to megakaryocyte colonies.

This rejection would be overcome by an evidentiary showing that the cells of Clay et al. are not monopotent when cultured in applicants' methylcellulose myeloid differentiation medium.

No claims are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Lora E Barnhart
Patent Examiner